REMARKS

Entry of this amendment and reconsideration of the rejection of the claims is respectfully requested.

Claims 77-78, 121-130, and 132 have been cancelled without prejudice or disclaimer. Claims 121-130 are cancelled due to a restriction requirement and applicants reserve the right to pursue the subject matter of these claims in a divisional application. Applicants reserve the right to pursue the subject matter of claims 77-78 and 132 in one or more continuation applications

Claims 55, 70-71, 89, and 105 are currently amended to clarify the subject matter of the claims. These amendments are supported throughout the specification including at page 34, lines 3-8 and page 35, lines 19-30. No new matter is introduced by these amendments.

Interview Summary

Applicants thank Examiner Crowder and her supervisor for the interview on October 9, 2007. We discussed the art rejections of record.

Restriction

The Examiner indicated that claims 86, 100, and 121-130 have been withdrawn from consideration as being drawn to nonelected inventions.

While not acquiescing to the statements by the Examiner and solely to expedite prosecution, Applicants have cancelled claims 121-130 without prejudice or disclaimer.

With regard to claims 86 and 100, Applicants submit that these claims were withdrawn from examination due to species election requirement. Applicants request rejoinder of the claims and examination if the elected species is found allowable.

Objection to the Claims

Claim 132 was objected to for being dependent on non elected claims. While not acquiescing to the rejection and solely to expedite prosecution, claim 132 has been cancelled rendering the rejection moot.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 55, 58-68, 70-85, 87–99, 101, 103-105, 107-113,131 and 132 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Claims 77-78, and 132 have been cancelled rendering the rejection of these claims moot. Applicants respectfully traverse the rejection with regard to claims 55, 58-68, 70-76, 79, 83-85, 87-99, 101, 103-105, 107-113 and 131.

Specifically, the Examiner contends that the specification fails to support the phrase "cysteine residue forms an inter-chain disulfide chain when present". While not acquiescing to the rejection and solely to expedite prosecution, the claims no longer refer to "forms". Applicants request withdrawal of the rejection

Rejections under 35 U.S.C. § 102(b)

Claims 55, and 58 were rejected under 35 U.S.C. § 102(b) as anticipated by Gillies et al., *Human Antibody Hybridomas* 1: 47–54 (1990), and by Davis et al., *EMBO J.* 9: 2519–2526 (1989). Applicants respectfully traverse this rejection.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Because neither Gillies nor Davis teach each and every element of the claims, they do not anticipate the claimed subject matter.

Gillies, inter alia, does not teach an isolated polynucleotide comprising a prokaryotic secretion signal sequence. Gillies et al teaches a construct expressed in a hybridoma cell line. Therefore, as Gillies fails to teach each and every element of the present claims, the reference does not anticipate the present claims.

Davies et al, inter alia, does not teach an isolated polynucleotide comprising a prokaryotic secretion signal sequence. Davies et al teaches a construct expressed in a hybridoma cell lines. Therefore, as Davis fails to teach each and every element of the present claims, the reference does not anticipate the present claims.

Based on the foregoing, withdrawal of the rejections under 35 U.S.C. § 102(b) is respectfully requested.

Rejection under 35 U.S.C. § 102(e)

Claims 55, 58–68, 70-85, 87–99, 101,103-105, 107-113 and 131-32 were rejected under 35 U.S.C. § 102(b) as anticipated by Simmons et al. (U.S. Patent Pub. No. 2005/0170464). Applicants respectfully traverse this rejection.

The present claims are directed to an isolated polynucleotide comprising a polynucleotide encoding a prokaryotic secretion signal sequence and a polynucleotide encoding an intact antibody comprising a variant heavy chain wherein the variant heavy chain comprises a variant hinge region which does not form inter-heavy chain disulfide linkages, and wherein said variant hinge region lacks a cysteine residue, wherein the cysteine residue is capable of forming an inter-chain disulfide linkage when present.

Applicants submit that when the Simmons reference is read as a whole, it does not disclose every element of the claims. The Simmons reference is directed to methods for improved expression and production of biologically active antibodies by using separate cistrons under the control of separate promoters and including separate translation initiation regions. The reference indicates that a cysteine residue not involved in maintaining the proper conformation of the antibody can be substituted by serine residues. It is important to note the reference does not state that any cysteine residue can be altered but those that are not involved in maintaining proper conformation of the antibody.

The Simmons et al reference describes the structure of full length antibodies throughout the document including at paragraph [0044] by stating "A naturally occurring antibody comprises four polypeptide chains, two identical heavy (H) chains and two identical light (L) chains, inter-connected by disulfide bonds." (emphasis added) At paragraph [0049] the reference states "The capability of a full length antibody to exert one or more of its natural activities depends on several factors, including proper folding and assembly of the polypeptide chains. As used herein, the biologically active immunoglobulins generated by the disclosed methods are typically heterotetramers having two identical L chains and two identical H chains that are linked by multiple disulfide bonds and properly folded." (emphasis added) At

paragraph [0103], the Simmons et al reference further states "Sufficient disulfide bonds are particularly important for the formation and folding of full length, bivalent antibodies having two heavy chains and two light chains." (emphasis added) Applicants submit when the Simmons reference is read as a whole, cysteine residues that form disulfide bonds that interconnect two heavy and light chains are involved in maintaining the proper conformation of a full length antibody. Therefore, the Simmons et al reference does not teach that an intact antibody can or should be produced wherein the variant heavy chain comprises a variant hinge region which does not form inter-heavy chain disulfide linkages, and wherein said variant hinge region lacks a cysteine residue, wherein the cysteine residue is capable of forming an inter-chain disulfide linkage when present as claimed by Applicants.

Secondly, Applicants submit that the Simmons et al reference indicates that a cysteine residue not involved in maintaining the proper conformation of the antibody can be substituted, generally by serine residues, to improve the oxidative stability of the molecule and prevent aberrant crosslinking. One of skill in the art reading the Simmons et al reference would understand that aberrant crosslinking can occur when cysteines in the hinge region form intradomain rather than the inter heavy chain domain cross links. Brennan et al, Science 229:81 (1985) In addition, it is known to those of skill in the art that formation of proper disulfide bonds increases oxidative stability. See Missiakas et al, Journal of Bacteriology 179:2465 (1997) Thus, the Simmons reference as a whole does not disclose a polynucleotide that encodes an intact antibody comprising a variant heavy chain comprising a variant hinge region which does not form inter-heavy chain disulfide linkages, and wherein said variant hinge region lacks a cysteine residue, wherein the cysteine residue is capable of forming an inter-chain disulfide linkage when present could provide for an intact antibody in high yield.

Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §103(a)

Claims 55, 57–85, 87–99, 101 and 103–114 were rejected under 35 U.S.C. § 103(a) as unpatentable over Gillies et al. and Davis et al., in view of Georgiou et al. (U.S. Patent No. 5,264,365) and Kurokawa et al., *J. Biol. Chem.* 276:14393–14399 (2001). Claims 77-78, 80-82 and 132 have been cancelled rendering the rejection of these claims moot. Applicants

respectfully traverse the rejection with regard to claims 55, 58-68, 70-76, 79, 83-85, 87-99, 101, 103-105, 107-113 and 131.

To make a *prima facie* case of obviousness, "it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." *Id.* The initial burden to make a *prima facie* case of obviousness is on the Examiner. *In re Bell*, 991 F.2d 781, 783 (Fed. Cir. 1993). Applicants submit that the Examiner does not make a *prima facie* case of obviousness, because all the limitations of the present claims are not taught by the combination of references cited in the Office Action and one of skill in the art would not have a reason to combine the references.

The present claims are directed to an isolated polynucleotide comprising a polynucleotide that encodes a prokaryotic secretion signal sequence and a polynucleotide encoding an intact antibody comprising a variant heavy chain, wherein the variant heavy chain comprises a variant hinge region which does not form inter-heavy chain disulfide linkages, and wherein the variant hinge region lacks a cysteine residue, wherein the cysteine residue is capable of forming an inter-heavy chain disulfide linkage when present.

The arguments and remarks provided above with respect to the Gillies and Davis references are also fully relevant here and are incorporated by reference to avoid repetition. To briefly summarize, Gillies fails to teach or suggest an isolated polynucleotide comprising a prokaryotic secretion signal sequence. Davis fails to teach or suggest an isolated polynucleotide comprising a prokaryotic secretion signal sequence. Georgiou is directed to construction of protease deficient *E. coli* hosts used to produce proteolytically sensitive peptides. Kurokawa describes production of NGF in *E. coli*, and the effect of Dsb protein overexpression on NGF production. None of these references, when combined, teach or suggest a polynucleotide comprising a polynucleotide encoding a prokaryotic secretion signal sequence and a polynucleotide encoding an intact antibody comprising a variant heavy chain, wherein the variant heavy chain comprises a variant hinge region that does not form inter-heavy chain disulfide linkages.

Moreover, one of skill in the art would not have a reason to combine these references. Gillies is focused on the interaction of effector functions and antigen binding of these constructs

produced in hybridoma cells. Gillies does not discuss whether these antibody constructs affect heavy chain aggregation or can increase antibody production. In fact, expression of the antibody constructs as described by Gillies et al shows formation of a heavy chain dimer due to aberrant crosslinking between the cysteines that normally are cross linked to the light chain. See figure 5. In addition, Gillies et al indicates that they did not form an intact antibody from the construct in which the cysteines were mutated. Thus, one of skill in the art interested in producing an intact antibody would not follow the teachings of Gillies because they did not produce any intact antibody. In addition, Gillies does not teach or suggest that intact antibodies can be produced in prokaryotic cells. As discussed in Missiakas et al, the production of disulfide containing proteins in bacteria is complex and susceptible to environmental factors.

The deficiency of Gillies is not remedied by reference to Georgiou, the '365 patent. The '365 patent does not describe production of intact antibodies nor does it describe or show a construct with a prokaryotic secretion signal sequence. The exemplified protein was a fusion of two bacterial proteins therefore it is unclear whether such secretion signal sequence was present or whether such secretion signal sequence would function to provide for secretion of intact antibodies as claimed by applicants.

The deficiency of Gillies is also not remedied by reference to Kurokawa et al. The Kurokawa et al reference is directed to expression of nerve growth factor and enhancement of disulfide bond formation. This reference does not teach or suggest a polynucleotide that encodes a prokaryotic secretion signal sequence and a polynucleotide encoding an intact antibody comprising a variant heavy chain, wherein the variant heavy chain comprises a variant hinge region which does not form inter-heavy chain disulfide linkages. The Kurokawa reference describes enhancing the disulfide bond formation.

Davis describes assembly of IgM subunits. Davis fails to teach or suggest an isolated polynucleotide comprising a prokaryotic secretion signal sequence. In addition, Davis et al. does not teach or suggest that intact antibodies can be produced in prokaryotic cells. As discussed in Missiakas et al., the production of disulfide containing proteins in bacteria is complex and susceptible to environmental factors.

The deficiency of Davis is not remedied by reference to Georgiou, the '365 patent. The '365 patent does not describe production of intact antibodies nor does it describe or show a construct with a prokaryotic secretion signal sequence. The exemplified protein was a fusion of two bacterial proteins therefore it is unclear whether such secretion signal sequence was present or whether such secretion signal sequence would function to provide for secretion of intact antibodies as claimed by applicants.

The deficiency of Davis is also not remedied by reference to Kurokawa et al. The Kurokawa et al reference is directed to expression of nerve growth factor and enhancement of disulfide bond formation. This reference does not teach or suggest a polynucleotide that encodes a prokaryotic secretion signal sequence and a polynucleotide encoding an intact antibody comprising a variant heavy chain, wherein the variant heavy chain comprises a variant hinge region which does not form inter-heavy chain disulfide linkages. The Kurokawa reference describes enhancing the disulfide bond formation.

In view of the remarks above, the rejection under 35 U.S.C. § 103(a) is believed to be overcome. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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